

# Schäfer. (L)



On the detection of small quantities of

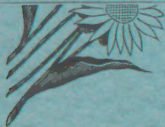
CINCHONIDINE

—IN—

Sulphate of Quinine

—BY—

DR. LOUIS SCHÄFER



*With the firm of C. F. BOEHRINGER & SOEHNE,  
Mannheim and New York, Manufacturers of Quinine and  
other Alkaloids.*



American Branch House,  
49 CEDAR STREET,  
NEW YORK.  
L. ENGELHORN, ATTY.



New York, May, 1887.

P. P.

In presenting you with this treatise on the purity of Quinine, we also beg to call your attention to the fact that we are now in position to supply the trade with a Quinine answering all the requirements of the referred to test, as we have been actively engaged in the manufacture of such Quinine for some time.

We have introduced this Quinine in Europe under the name of "Chinin. Sulfuricum Purissimum," and are gratified to say that the trade, recognizing its merits, have received it very favorably, and that it is already demanding a large sale, especially in France, where the Pharmacopoeia imposes a more rigorous test.

We trust that in placing it on the American market it will be similarly received, and that it will meet with the attention of the trade.

Considering the purity of this Quinine, the slight advance

charged on it, is very unimportant, especially to those desirous of obtaining a purer drug.

Our price to-day for :

***“Quinine Sulph. Puriss” Boehringer,  
in 1 oz. vials is 70c., incl.***

at which figure we shall be pleased to furnish sample bottles to any of our friends desirous of examining or analyzing same.

We also take this opportunity of calling the attention of the trade to the following line of fine chemicals manufactured by us, and which can be had from nearly every wholesale druggist in the United States :

Sulphate of Quinine and its Salts,  
Quinidia and Cinchonidia,  
Sulph. of Cinchonina,  
Acetanilid (Antifebrin),  
Atropia,  
Cocaine and its Salts,  
Salicine,  
Urethan,

Codein Pure.  
Ergotine “  
Caffein,  
Sulph. of Morphia,  
Eserine,  
Pilocarpine,  
Terpinhydrat,  
Veratrin,

&c., &c., &c.


In ordering please specify “Boehringer & Soehne,” and do not allow other brands of Quinine to be substituted which may be offered under a similar name.

Soliciting your favorable attention, we are

Yours very truly,

**C. F. Boehringer & Soehne.**



HE directions given by the United States Pharmacopoeia for ascertaining the purity of Quinine Sulphate, *are accompanied by a note stating that if the drug answers to the prescribed test, it will not contain more than one per cent. of Cinchonidine or Quinidine, and not more than traces of Cinchonine.* I have been recently engaged in making a number of experiments with this test, and the results I have obtained clearly show that it is not by any means so rigorous in its indications as this note represents it to be. So far as Quinidine and Cinchonine are concerned the statement is true ; but the sulphates of these alkaloids are so easily and completely separated from Sulphate of Quinine in the processes of recrystalization by which manufacturers refine the latter salt, that they are never found in the Quinine of commerce unless they have purposely or accidentally been added. It is otherwise with Cinchonidine. Most of the salts of Quinine and Cinchonidine so persistently crystallize together, even when there is a considerable difference in their solubilities, *that commercial Quinine commonly retains more or less of this alkaloid.* It follows that Cinchonidine is the impurity which it is most important to recognize with precision in determining the quality of Quinine, yet it is precisely here that the test of the United States Pharmacopoeia fails in its delicacy. So far from its indicating with any accuracy more than one per cent. of Cinchonidine, I find *that nearly ten per cent. may escape recognition.*

In examining this test it is very important to make the

difference in the results obtained when (1) varying quantities of Cinchonidine Sulphate are merely added to Quinine Sulphate before applying the test, and when (2) the two sulphates are *brought into intimate contact or crystallized together* before the application of the test. In the former case the test furnishes fairly correct indications, in the latter, it fails. The following experiments will illustrate this :—Some chemically pure Quinine Sulphate was prepared by re-crystallizing some kilogrammes of good Quinine as bi-sulphate and then as neutral sulphate. Several small portions of this pure sulphate were taken and a varying quantity of Cinchonidine Sulphate added to each. These portions were dried at 100°C. for some hours, and then transferred to small beakers, care being taken to mix the sulphate as little as possible in these operations. Ten parts of distilled water were added to each and maceration conducted at 18°C. with occasional stirring for half an hour. The liquid was then filtered off and to 5 c. c. of each filtrate, Solution of Ammonia sp. gr. .960 was added until a clear liquid resulted :—

5 c. c. of the filtrate			required c. c. of ammonia.	
Chemically pure Quinine Sulphate				4.75.
do	do	+ 1% Cinchonidine Sulphate,	5.50.	
do	do	+ 2%	“ “	6.50 to 6.75.
do	do	+ 3%	“ “	7.75.
do	do	+ 5%	“ “	10.75.
do	do	+ 8%	“ “	14.00.

The three following experiments were then made :—

**A.** 1.84 gramme of chemically pure Quinine Sulphate, and 0.16 gramme of Cinchonidine Sulphate were dried at 100°C. for three hours and transferred to a beaker glass, the rinsing of the sulphate being avoided as much as possible. After maceration with occasional stirring for half an hour at 18°C. in 20 c. c. of water, the liquid was filtered off and 5 c. c. of the filtrate required 14 c. c. of Solution of Ammonia to form a clear liquid ; thus confirming the result obtained in the preceding series.

**B.** 1.84 gramme of the Quinine Sulphate and 0.16 gramme of Cinchonidine Sulphate were intimately rubbed together in a mortar. The mixture dried for three hours at 100°C. and macerated in 20 c. c. of water exactly as before. 5 c. c. of the filtrate gave a clear solution when only 9 c. c. of the ammonia had been added.

**C.** 1.84 gramme of the Quinine Sulphate and 0.16 gramme of Cinchonidine Sulphate were first dried at 100°C. for three hours and then well rubbed together in a mortar, transferred to a beaker and macerated in 20 c. c. of water exactly as the others were treated. 5 c. c. of the filtrate took only 7 c. c. of ammonia to yield a clear liquid.

In experiment A. the Cinchonidine Sulphate was able to pass into solution before the affinity between the two salts had been exerted ; but in B. & C. where the two Sulphates were brought into more and more intimate contact before maceration, less and less of the Cinchonidine was taken up by the

water. It is easy to conceive that the results of experiments such as those in the first series would lead to an erroneous conception of the delicacy of the test ; and it may be that it was upon trials similarly conducted that the statement in the United States Pharmacopoeia was based. But the results of experiments B. & C. clearly show that the conception is erroneous. When the Cinchonidine has crystallized out with the Quinine, as would always be the case in the Quinine of commerce, the two salts are in the most intimate contact possible, and then the indications obtained by the test are much below the truth. The foregoing results indicate not only the fallacy in this test but in *all tests in which the Quinine to be examined is not brought into complete solution*. It is only when perfect solution is effected that the results are comparable with those obtained from specially prepared mixtures.

There has been a general desire of late to find a method for the examination of Quinine by which the presence of one per cent of Cinchonidine could be indicated with some certainty. I have made a careful investigation of the various processes hitherto published and have tried many modifications of them, with a view of ascertaining how far they might be fit for this purpose. (The results of my observations were published in the Archiv der Pharmacie 1886, Heft 19 H.) The conclusion deducible from my experiments was that none of these methods could be trusted for the detection of so small a proportion as one per cent. Even the new test of the well known Quinologist, Dr. J. E. de Vry, with Chromate of



Potassium failed to fulfil this condition. But further investigation of the subject has enabled me to find a test which will accomplish the desired object. It is this test which I now desire to bring under the notice of American chemists.

Its action depends on the extremely slight solubility of Quinine oxalate in a dilute solution of Potassium oxalate and the comparatively free solution of Cinchonidine oxalate under like circumstances. The mode of operation is as follows:—

Two grammes of the Quinine Sulphate to be examined are placed in a small tared flask with 60 c. c. of distilled water. The contents of the flask are raised to the boiling point and maintained at that temperature until solution is effected. 0.5 grammes of neutral crystallized Potassium oxalate, previously dissolved in 5 c. c. of water is then added and mixed with the solution of the sulphate by shaking the flask. Sufficient water is then introduced to bring the total weight of the contents up to 67.5 grammes. (This is done to replace the water lost in boiling.) The flask is then cooled to 20°C., by standing it in water at that temperature, and occasionally shaken. After half an hour, the contents are filtered. To the clear filtrate a drop of solution of caustic soda is added; if the liquid remains clear and bright, the original sulphate contained less than one per cent. of Cinchonidine. When one per cent. or more is present, the liquid becomes opalescent or yields a precipitate. This test recommends itself by its simplicity. It can be readily performed with the most common appliances in less than an hour, and its indications are trustworthy. It can

also be adapted by some modification to the quantitative estimation of the Cinchonidine. The presence of both Cinchonine and Quinidine are also indicated by it.

I add that this test is somewhat more rigorous if the sulphate is dissolved in 55 c. c. of water and the total weight of the contents of the flask is brought up to 62.5 grammes. Occasionally with this proportion an unimportant quantity of the sulphate dissolves rather slowly.

The Potassium Oxalate for this test shall have only a feeble alkaline reaction. I prepared it dissolving pure oxalic acid in water, adding gradually pure Carbonate of Potassium until the solution had a faint acidulous reaction on litmus. I evaporated until crystals began to form, collected the crystallized Potassium Oxalate and dried it.

I may take this opportunity of adding that pure Quinine Sulphate which will stand this test can be prepared in the same loose light silky crystals that have become the recognized characteristic of this important drug. The assertion so often made that chemically pure Quinine Sulphate only crystallizes in hard needles I cannot confirm. This is of great importance because it is not necessary to give up the characteristic loose form of the Quinine Sulphate if the Pharmacopoeia requires a purer salt. Messrs. C. F. Boehringer & Soehne, of Mannheim were the first to supply commerce with a pure Quinine Sulphate in this condition. Their "*Quininae Sulfas puriss*" satisfies completely the test above described.



